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SHORT COMMUNICATION

Ophthalmologic abnormalities in long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: Presentation of a long-term survivor

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PURPOSE. *Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency is one of the recently discovered defects of mitochondrial fatty acid beta-oxidation surprisingly associated with ophthalmologic abnormalities. The presentation of a long-term survivor may enlarge the clinical spectrum associated with this disorder.*
METHODS. *A 12-year retrospective review of the clinical course of a 19-year-old long-term survivor was performed. The author concentrated on characteristic ophthalmologic measures: visual acuity, refraction, ophthalmoscopy, visual fields, and electroretinography.*
RESULTS. *The author found a milder course than described in the literature, although very few case reports of long-term survivors have been published. The patient developed slower circumscribed atrophy of the choroid, retinal pigment epithelium, and retina.*
CONCLUSIONS. *Because of therapeutic and prenatal diagnostic opportunities in LCHAD deficiency, it is important to recognize this severe disorder early in its course. This may lead to a milder course and better prognosis due to early dietary therapy. (Eur J Ophthalmol 2008; 18: 476-8)*

KEY WORDS. *LCHAD deficiency, Beta-oxidation defect, Chorioretinopathy, Hereditary metabolic disorder*

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INTRODUCTION

Defects of mitochondrial fatty acid beta-oxidation are amongst the most common inherited metabolic disorders. Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency is one of the recently discovered defects of fatty acid beta-oxidation (1). Surprisingly, ophthalmologic abnormalities have only been reported in patients with LCHAD deficiency (2-5). Very few case reports and small series of patients have been published, in most cases patients who died very early.

METHODS

A 12-year retrospective review of the clinical course of a 19-year-old long-term survivor was performed. Diagnosis of a fatty acid oxidation disorder was suggested in her later childhood because of recurrent hypoketotic hypoglycemia, rhabdomyolysis, carnitine deficiency, and increased amounts of dicarboxylic acids in the urine. The patient initially had rather nonspecific chronic symptoms such as mild failure to thrive and feeding difficulties. Confirmation of the specific diagnosis caused by the common mutation G1528C was performed by mutational analysis and by measuring LCHAD activity in lymphocytes at age 8. We concentrated on characteristic ophthalmologic measures: visual acuity, refraction, ophthalmoscopy, visual fields, and electroretinography. In the beginning the child was followed once a year in the clinic, later on every second year.

RESULTS

Once the diagnosis was established the patient was treated with a low-fat, high-carbohydrate diet. In addition she

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started with a medium-chain triglycerides (MCT)-enriched diet and L-carnitine. Avoidance of prolonged fasting was strictly recommended.

She was referred to an ophthalmologist. The fundus appearance at the age of 8 was clearly abnormal. The peripapillary retinal pigment epithelium (RPE) was atrophic. Toward the midperiphery a coarsely granular aspect of the RPE with some isolated pigment clumps was apparent. The arteries were slightly narrow, but the optic disks did not show any paleness. The electroretinogram (ERG) showed significant reduction of amplitudes in the pattern ERG and slightly reduced amplitudes in the flash ERG. Nonetheless the first visual fields recorded with the Goldmann kinetic perimeter were roughly normal.

Development of best-corrected visual acuity and refractive error is seen in Table I.

For 9 years the ophthalmologic findings did not change dramatically corresponding to the subjective perception of the patient. However, slowly progressive chorioretinal atrophy starting from the peripapillary region occurred, sparing the posterior pole. This finding was confirmed by gradual deterioration of visual acuity, visual fields, and ERG. Pattern ERG became isoelectric when the patient was 17 and flash ERG was subnormal. Only myopia showed distinct progression (Tab. I).

When we saw the patient at 19 years of age, her visual abilities had remarkably decreased. The pigmentary retinopathy had further progressed, sparing a central island of the remaining choroids and photoreceptors of her right eye only and showing the bilateral peripheral fundus relatively maintained. Amplitudes of the flash ERG went further down. The visual field of the right eye (V/4) showed a paracentral ring-shaped scotoma with a horizontal diameter of 40° with central sparing. In the left she already had a central scotoma with a horizontal diameter of 45°. The patient had always been orthotropic with normal ocular motility.

The anterior segment was unremarkable in all examinations. Lens opacities as described in other patients was not detected even when searched for specifically.

TABLE I - DEVELOPMENT OF BEST-CORRECTED VISUAL ACUITY AND REFRACTIVE ERROR OVER TIME

Age (yrs)	Visual acuity	Refraction
8	R: 0.63	R: –1.25 –1.5 120°
	L: 0.32	L: –1.5 –0.75 30°
9	R: 0.5	R: –2.0 –0.5 140°
	L: 0.25	L: –1.75 –0.75 25°
11	R: 0.63	R: –2.5 –1.75 135°
	L: 0.25	L: –3.0 –1.75 30°
13	R: 0.5	R: –5.5 –1.5 135°
	L: 0.1	L: –5.5 –1.5 25°
15	R: 0.5	R: –6.0 –1.0 135°
	L: 0.2	L: –6.0 –1.0 30°
17	R: 0.4	R: –7.5 –0.5 130°
	L: 0.2	L: –7.5 –1.5 20°
19	R: 0.3	R: –7.5 –1.0 135°
	L: 0.05	L: –7.25 –175 20°

DISCUSSION

In most patients with LCHAD deficiency the disease presents prior to the age of 3 years (2). In many cases the disease leads to death during the first years of life. In the majority of patients the disease presents with an acute metabolic derangement with hypoketotic hypoglycemia. Less typical is a presentation in form of a more chronic disorder (2).

In contrast our patient initially had almost no symptoms and diagnosis was established because of recurrent hypoketotic hypoglycemia when she was 8 years old. This might have indicated a milder form early.

In general we could confirm the clinical features found in patients with LCHAD deficiency: normal fundus at birth, followed by pigment dispersion in the RPE and complicated by circumscribed chorioretinal atrophy, occlusion of choroidal vessels with relative sparing of the peripheral fundus (stages 1 to 4 of Tyni et al) (3).

Tyni et al (3) reported on four patients with long-term survival. Two of them, age 5, were diagnosed early. The other two patients reported are a 16-year-old girl and a 31-year-old man with delayed dietary therapy because of late diagnosis at age 4. At the age of 8 the girl only had attenuated remnants of large choroidal vessels in the posterior pole. Seven years later an almost bare sclera remained in the posterior pole and posterior staphylomas were present bilaterally. The clinical course and the fundus changes of the 31-year-old man corresponded roughly to those detected in the girl with final atrophic area of the central fundus and posterior staphylomas. However, structures were preserved longer and the course similar to that seen in our patient.

Our patient developed slower circumscribed atrophy of

the choroid, RPE, and retina. She had progressive myopia. The ERG initially was almost normal but later was less recordable. At last presentation we found atrophy of the choroid in the posterior pole, leaving the sclera bare and the larger choroidal vessels sclerotic (stage 3 of Tyni et al) (3).

The pathogenesis of the ocular manifestation in patients with LCHAD deficiency is not clearly understood. The molecular genetic defect of LCHAD deficiency is characterized and the clinical findings, fluorescein angiography, and ERG suggest a primary defect at the level of the RPE and choriocapillaris (3, 6). Furthermore, there is some evidence for a primarily affected RPE due to the hypothesis that mitochondrial fatty acid β-oxidation is involved in metabolism of the RPE (7).

Presentation of our long-term survivor with a better course may enlarge the clinical spectrum associated with this disorder. Because of therapeutic and prenatal diagnostic opportunities in LCHAD deficiency, it is important to recognize this severe disorder early in its course.

The authors have no proprietary interest.

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